

BENEFIT OF CAROTID ENDARTERECTOMY IN PATIENTS WITH SYMPTOMATIC MODERATE OR SEVERE STENOSIS

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ABSTRACT

Background Previous studies have shown that carotid endarterectomy in patients with symptomatic severe carotid stenosis (defined as stenosis of 70 to 99 percent of the luminal diameter) is beneficial up to two years after the procedure. In this clinical trial, we assessed the benefit of carotid endarterectomy in patients with symptomatic moderate stenosis, defined as stenosis of less than 70 percent. We also studied the durability of the benefit of endarterectomy in patients with severe stenosis over eight years of follow-up.

Methods Patients who had moderate carotid stenosis and transient ischemic attacks or nondisabling strokes on the same side as the stenosis (ipsilateral) within 180 days before study entry were stratified according to the degree of stenosis (50 to 69 percent or <50 percent) and randomly assigned either to undergo carotid endarterectomy (1108 patients) or to receive medical care alone (1118 patients). The average follow-up was five years, and complete data on outcome events were available for 99.7 percent of the patients. The primary outcome event was any fatal or nonfatal stroke ipsilateral to the stenosis for which the patient underwent randomization.

Results Among patients with stenosis of 50 to 69 percent, the five-year rate of any ipsilateral stroke (failure rate) was 15.7 percent among patients treated surgically and 22.2 percent among those treated medically ($P=0.045$); to prevent one ipsilateral stroke during the five-year period, 15 patients would have to be treated with carotid endarterectomy. Among patients with less than 50 percent stenosis, the failure rate was not significantly lower in the group treated with endarterectomy (14.9 percent) than in the medically treated group (18.7 percent, $P=0.16$). Among the patients with severe stenosis who underwent endarterectomy, the 30-day rate of death or disabling ipsilateral stroke persisting at 90 days was 2.1 percent; this rate increased to only 6.7 percent at 8 years. Benefit was greatest among men, patients with recent stroke as the qualifying event, and patients with hemispheric symptoms.

Conclusions Endarterectomy in patients with symptomatic moderate carotid stenosis of 50 to 69 percent yielded only a moderate reduction in the risk of stroke. Decisions about treatment for patients in this category must take into account recognized risk factors, and exceptional surgical skill is obligatory if carotid endarterectomy is to be performed. Patients with stenosis of less than 50 percent did not benefit from surgery. Patients with severe stenosis (≥ 70 percent) had a durable benefit from endarterectomy at eight years of follow-up. (N Engl J Med 1998;339:1415-25.)

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IN 1954 a patient with symptoms suggesting that a stroke was imminent underwent successful removal of a stenosed segment of the carotid artery.¹ From that initial experience, carotid endarterectomy evolved. In 1985 it was performed 107,000 times in the United States.² Two negative randomized trials were reported.^{3,4} On the basis of anecdotal evidence, about 1 million endarterectomies were performed worldwide between 1974 and 1985.^{5,6}

Reports of unacceptable rates of complications, reviews of health care data bases, and editorials called into question the benefit of endarterectomy.⁷⁻¹³ The failure of cerebral bypass surgery in a randomized trial strengthened the opinion that data from case series alone were inadequate as a guide to the use of surgical therapy.¹⁴ Three studies of endarterectomy in patients with symptomatic carotid stenosis¹⁵⁻¹⁷ were intended to answer similar questions: How efficacious is endarterectomy as compared with medical care alone? Which patients should be offered endarterectomy? What is the acceptable complication rate? What bearing do risk factors have on benefit? How durable are the benefits of endarterectomy? Do other causes of stroke confound the interpretation of results?

In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), begun in 1987, we stratified patients according to the degree of stenosis: those with moderate stenosis, defined as less than 70 percent of the luminal diameter, and those with severe stenosis, defined as stenosis of 70 to 99 percent. In February 1991, after 659 patients with ≥ 70 percent

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stenosis had undergone randomization at 50 centers, the study in this stratum was stopped.^{15,18} Endarterectomy was found to be associated with an absolute reduction of 17 percentage points (95 percent confidence interval, 10 to 24) in the risk of ipsilateral stroke at two years. Consequently, endarterectomy was recommended for the patients with severe stenosis who had been randomly assigned to medical therapy.

Patients with moderate stenosis (<70 percent) continued to be enrolled. All patients with severe stenosis (≥ 70 percent) who were enrolled in the first phase were followed until the trial concluded. This report provides data on the outcomes of carotid endarterectomy in patients with moderate stenosis, enrolled from December 1987 through December 1996, and on the patients with severe stenosis who were enrolled through February 1991.

METHODS

Details of our research methods have been published elsewhere.¹⁹ Patients with moderate carotid stenosis were enrolled at 106 centers and stratified according to the degree of stenosis: high moderate (50 to 69 percent) or low moderate (<50 percent). The primary research question was this: For patients with moderate stenosis, is it better to perform endarterectomy immediately or to give medical therapy and offer endarterectomy only if stenosis progresses to 70 percent or more? Patients randomly assigned to medical therapy whose stenoses progressed to 70 percent or more, with symptoms, were offered endarterectomy.

Eligibility and Randomization

Patients over 80 years of age were excluded in the first phase (the study of both moderate and severe stenosis through February 1991) but included in the second phase (the continuing study of moderate stenosis). Patients were eligible if they had symptoms of focal cerebral ischemia ipsilateral to a stenosis of less than 70 percent in the internal carotid artery within 180 days, as shown on selective angiography, and persisting less than 24 hours or producing a nondisabling stroke (Rankin score <3 with symptoms for 24 hours or more).²⁰ All angiograms were assessed at the central office of the study with use of a magnifying eyepiece to measure the severity of carotid stenosis.^{19,21} Patients were excluded if they did not provide informed consent or if one or more of the following were present: lack of angiographic visualization of the symptomatic artery, intracranial stenosis that was more clinically significant than the cervical lesion, other disease that limited life expectancy to less than five years, cerebral infarction that eliminated useful function in the affected arterial territory, nonatherosclerotic carotid disease, cardiac lesions likely to cause cardioembolism, or a history of ipsilateral endarterectomy.

Patients were randomly assigned to medical or surgical therapy by means of a centralized computer-generated algorithm with stratification according to center.

Treatment

Patients were prescribed antiplatelet treatment (usually aspirin, with the dose left to the discretion of the neurologist at each study center) and, when indicated, antihypertensive and antilipidemic drugs. Surgical technique was left to the discretion of the individual surgeons. Simultaneous vascular procedures were discouraged.

Follow-up

Neurologists assessed all patients at entry, at 1, 3, 6, 9, and 12 months, and every 4 months thereafter. Risk-factor management

was monitored in the study data center. Cross-sectional brain imaging was performed after suspected cerebrovascular events. Duplex ultrasonography was repeated at one month, at intervals of one year after study entry, and after cerebrovascular events. If endarterectomy appeared to be indicated by noninvasive studies, angiography was repeated. Randomization ceased on December 15, 1996. Final assessments of patients took place between January 1 and December 15, 1997.

Events

We assessed the underlying cause of all deaths and the territory, type, severity, and duration of strokes. Strokes were considered disabling if patients had a Rankin score of 3 or more at 90 days. Outcome events were assessed in four steps: first, by the participating neurologist and surgeon; second, by the neurologists at the study data center; third, by the members of the steering committee, in a blinded manner; and fourth, by blinded external adjudicators. Lacunar strokes, as distinct from strokes of large-artery origin, were defined on the basis of a combination of clinical and radiologic criteria, as follows: events presenting with primary motor, primary sensory, or sensory-motor symptoms, the dysarthria-clumsy hand syndrome, or the ataxia-hemiparesis syndrome, all with radiologically deep white-matter lesions or basal-ganglia lesions <1 cm in diameter. The criteria for cardioembolic stroke included atrial fibrillation, myocardial infarction and its thrombotic or cardiac-wall sequelae, the need for cardiac interventional procedures, and the presence of valvular lesions. When the diagnosis was unclear, consultation with a cardiologist, with appropriate investigations, was requested.

Statistical Analysis

The primary intention-to-treat analysis compared medical and surgical patients in terms of the time to treatment failure (defined as a fatal or nonfatal ipsilateral stroke), with use of the Mantel-Haenszel chi-square test and Kaplan-Meier survival curves.²² The benefit of endarterectomy was described in terms of relative and absolute reductions in the risk of stroke and the number of patients who would need to be treated with endarterectomy for one outcome event to be prevented within five years after the procedure. Standard errors of the absolute risk reduction at five years and 95 percent confidence intervals for the survival curves were calculated with use of Greenwood's formula.²² In the primary analysis, treatment failure was defined as any fatal or nonfatal stroke ipsilateral to the carotid lesion. Secondary analyses included the end points of all strokes, all deaths, and strokes according to severity categories. All P values were two-tailed, and P values below 0.05 were considered to indicate statistical significance.

The primary and secondary analyses included all strokes (at any location) and all deaths (from any cause) that occurred during the 30-day postoperative period, or a 32-day period after randomization in the case of patients assigned to medical therapy. Patients discovered to be ineligible after randomization because they did not have a qualifying carotid lesion or corresponding symptoms were excluded from all analyses.

Risk factors for stroke and death in the 30 days after endarterectomy were evaluated in logistic-regression analyses. In these analyses, each of the base-line factors on which we obtained data was considered. Only univariate results are presented in this article.

The influence of base-line risk factors in determining which patients benefited most from carotid endarterectomy was investigated with use of Cox proportional-hazards regression modeling.²² To minimize the risk of chance findings and to increase the clinical relevance of the results, risk factors were considered important only if they differentiated between patients who benefited from endarterectomy and those who did not with respect to both any ipsilateral stroke and disabling ipsilateral stroke. Analyses of event-free survival were used to estimate the number of patients who would need to be treated in order to prevent one ipsilateral stroke during the five years after the procedure, among patients in various risk-factor categories.

RESULTS

Accrual of Patients

A total of 2267 patients with stenosis of less than 70 percent were randomly assigned to treatment groups. A review panel blinded to the treatment assignments excluded 41 patients (1.8 percent) because they did not meet the entry criteria; 24 of the 41 underwent endarterectomy because the central angiographic review showed the stenosis to be greater than 70 percent, 11 did not have angiographic evidence of stenosis, 3 did not have a qualifying ischemic event, 2 did not provide informed consent, and no information was available after randomization for 1. The remaining 2226 eligible patients (1118 assigned to medical therapy and 1108 to surgical therapy) were included in all analyses. The treatment groups were well balanced in terms of base-line characteristics (Table 1).

There were 858 eligible patients with 50 to 69 percent stenosis (428 in the medical-therapy group and 430 in the surgical-therapy group); 1368 had stenosis of less than 50 percent (690 in the medical-therapy group and 678 in the surgical-therapy group). Among the patients with low-moderate stenosis (<50 percent) there were 425 patients (213 in the medical-therapy group and 212 in the surgical-therapy group) who were found to have stenosis of less than 30 percent after angiographic review. These patients were included in all analyses reported here. Analyses performed with and without these patients with so-called mild stenosis did not differ significantly.

Follow-up

The average follow-up for all patients was five years. Six patients (five in the surgical-therapy group and one in the medical-therapy group) were lost to follow-up after a median of 36 months. Complete data about outcome events were available for 99.7 percent of the patients. All 1818 surviving patients (911 in the medical-therapy group and 907 in the surgical-therapy group) underwent final assessments during 1997.

Crossovers

Twenty-one (1.9 percent) of the 1108 patients randomly assigned to surgery did not actually undergo endarterectomy: 12 withdrew their consent, 6 had medical complications, and the surgeons decided not to perform endarterectomy in 3. All were followed throughout the study and included in all analyses except those involving the calculation of perioperative morbidity and mortality.

In the medical-therapy group, 88 of 1118 patients (7.9 percent) underwent endarterectomy, as specified in the protocol, after the progression of stenosis to 70 percent or more was verified by angiography; an additional 34 (3.0 percent) underwent endarterectomy after an ipsilateral stroke. Only 78 (7.0 percent)

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS WITH MODERATE STENOSIS, ACCORDING TO TREATMENT GROUP.*

CHARACTERISTIC	MEDICAL THERAPY (N = 1118)	SURGICAL THERAPY (N = 1108)
Median age (yr)	66	66
Age (%)		
<65 yr	36	41
65-74 yr	47	45
≥75 yr	17	14
Sex (%)		
Male	69	71
Female	31	29
Race (%)		
White	93	93
Black	3	4
Other	4	3
Qualifying event (%)		
TIA (hemispheric)	37	40
Stroke (hemispheric)	45	42
TIA (retinal)	13	12
Stroke (retinal)	5	6
Randomized within 30 days of event (%)	42	41
History of TIA or stroke (%)	55	54
Location of lesion (%)		
Right-sided	46	47
Left-sided	54	53
Degree of ipsilateral stenosis (%)		
50-69%	38	39
30-49%	43	42
<30%	19	19
Ipsilateral findings (%)		
Ulcerated or irregular plaque	51	51
Intracranial disease	32	33
Lesion on CT or MRI	43	46
Contralateral lesion (%)		
Occlusion	6	4
Ulceration	22	23
Diastolic blood pressure >90 mm Hg (%)	11	12
Systolic blood pressure >160 mm Hg (%)	19	20
History (%)		
Prior MI or angina	36	36
Hypertension	61	61
Diabetes	21	23
Hyperlipidemia	37	33
Intermittent claudication	15	15
Current cigarette smoking	31	31
Medications (%)		
Antithrombotic medication	98	97
Aspirin		
None	17	15
<650 mg/day	45	48
≥650 mg/day	38	37
Antihypertensive medication	60	61
Lipid-lowering medication	16	13
Cardiac medication	39	41

*TIA denotes transient ischemic attack, CT computed tomography, MRI magnetic resonance imaging, and MI myocardial infarction. There were no statistically significant differences between the groups in any of the base-line variables.

underwent endarterectomy not mandated by the protocol, often at the insistence of the patients or their attending physicians. Censoring the data on these 78 patients at crossover had no effect on our conclusions.

Medical Treatment

The medical treatment prescribed was similar in the two groups. The percentage of patients who were prescribed antithrombotic medications (mostly aspirin) was 96 to 99 percent in both groups throughout the trial. At base line, 37 percent of the patients were taking 650 mg or more of aspirin per day, and 11 percent were taking less than 325 mg. At the final follow-up evaluation, 31 percent were taking 650 mg or more per day. Antihypertensive medications were taken by 60 percent of the patients assigned to medical therapy at base line and 61 percent of the patients assigned to surgery; this proportion rose to 68 percent in both groups at the end of the study. Lipid-lowering medications were prescribed for 16 percent of the patients in the medical-therapy group and 13 percent of those in the surgical-therapy group at base line, a proportion that rose to 40 percent in both groups. Initially, cardiac medications were taken by 39 percent of the medical-therapy group and 41 percent of the surgical-therapy group; this proportion rose to 52 percent in both groups by the end of the study.

When blood pressure monitoring at the study data center identified diastolic readings of 90 mm Hg or more, systolic readings of 160 mm Hg or more, or both, at two consecutive follow-up clinic visits, letters went to the neurologists at the center where the patient was followed, alerting them to the patient's hypertension. The prevalence of hypertension declined from 15 percent to 10 percent in both treatment groups over the course of the trial.²³

Perioperative Morbidity and Mortality

A total of 1108 patients were randomly assigned to endarterectomy; 21 of these received only medical therapy, and endarterectomy was scheduled for 1087. Between randomization and endarterectomy, one retinal stroke occurred; there were no deaths. A median of two days elapsed between randomization and endarterectomy. Endarterectomy was incomplete in three patients.

In the 30 days after endarterectomy, 73 of the 1087 patients who underwent endarterectomy (6.7 percent) had a stroke or died. Forty-three (4.0 percent) had a nondisabling stroke (Rankin score, <3), 17 (1.6 percent) had a nonfatal, disabling stroke (Rankin score, ≥3), and 13 (1.2 percent) died (7 of stroke, 3 of wound complications, 2 of myocardial infarction, and 1 suddenly on day 3). In the 32 days after randomization, 27 medically treated patients (2.4 percent) had a stroke or died; 1.4 percent had disabling stroke or died. The net increase in risk at 30 days associated with surgery was 4.3 percent for any stroke or death,

and 1.4 percent for disabling stroke or death. In eight patients in the surgical-therapy group who had a stroke, the severity decreased from disabling to non-disabling by 90 days, yielding a rate of perioperative disabling stroke and death of 2.0 percent.

Outcome Events

Table 2 shows the five-year risk of treatment failure, defined according to six sets of criteria, for each category of the severity of stenosis (50 to 69 percent vs. <50 percent). For the primary analysis of any fatal or nonfatal ipsilateral stroke, the five-year failure rate for patients with 50 to 69 percent stenosis was 22.2 percent for medically treated patients and 15.7 percent for surgically treated patients ($P=0.045$). The absolute difference of 6.5 percentage points corresponded to a relative risk reduction of 29 percent (95 percent confidence interval, 7 to 52 percent); 15 patients would need to be treated by endarterectomy to prevent one ipsilateral stroke at five years. For patients with stenosis of less than 50 percent, the corresponding five-year failure rates were 18.7 percent for medically treated patients and 14.9 percent for surgically treated patients ($P=0.16$).

This pattern persisted for all six definitions of treatment failure. Patients with 50 to 69 percent stenosis were at greater risk when treated medically, and obtained a greater benefit from surgery, than patients with stenosis of less than 50 percent. Among patients with 50 to 69 percent stenosis, the Mantel-Haenszel chi-square test was at or near statistical significance for all six definitions. It never approached significance for the patients with stenosis of less than 50 percent.

Figure 1 shows the curves for event-free survival. Among the patients enrolled who had stenosis of 70 percent or more, the 95 percent confidence intervals for the curves remain separate at all times, whether the outcome in question is stroke of any degree of severity or disabling stroke. Among the patients with 50 to 69 percent stenosis, the confidence intervals overlap slightly at all times. The overlap is greater for disabling stroke than for any stroke. The confidence intervals totally overlapped among the patients with stenosis of less than 50 percent. The increasing overlap in the confidence intervals coincides with larger P values, indicating decreasing significance.

Among patients treated surgically, the risk of ipsilateral stroke dropped within 10 days after endarterectomy to about 2 percent per year (Fig. 2). Among medically treated patients, the risk of ipsilateral stroke, which was highest immediately after the initial ischemic event, dropped more gradually to about 3 percent per year within two to three years. This was true both for patients with moderate stenosis (50 to 69 percent) and for those with severe stenosis (70 to 99 percent).

Secondary analysis according to deciles of stenosis did not show a gradient of benefit. The distribution

TABLE 2. FAILURE RATES AT FIVE YEARS OF FOLLOW-UP, ACCORDING TO THE EVENT DEFINING TREATMENT FAILURE, IN PATIENTS WITH MODERATE STENOSIS.

EVENT DEFINING TREATMENT FAILURE*	MEDICAL THERAPY	SURGICAL THERAPY	RELATIVE REDUCTION IN RISK	ABSOLUTE REDUCTION IN RISK†	P VALUE‡	NUMBER NEEDED TO TREAT§
	no. of first events (failure rate)¶		percent			
Stenosis 50–69%						
No. of patients	428	430				
Any ipsilateral stroke	80 (22.2)	57 (15.7)	29	6.5±3.0	0.045	15
Disabling ipsilateral stroke	24 (7.2)	11 (2.8)	61	4.4±1.7	0.054	23
Any stroke	113 (32.3)	85 (23.9)	26	8.4±3.5	0.026	12
Any disabling stroke	34 (10.3)	20 (5.3)	49	5.0±2.1	0.070	20
Any stroke or death from any cause	156 (43.3)	120 (33.2)	23	10.1±3.8	0.005	10
Any disabling stroke or death from any cause	86 (25.2)	64 (18.3)	27	6.9±3.2	0.032	14
Stenosis <50%						
No. of patients	690	678				
Any ipsilateral stroke	110 (18.7)	89 (14.9)	20	3.8±2.3	0.16	26
Disabling ipsilateral stroke	27 (4.7)	27 (4.6)	3	0.1±1.3	0.95	1000
Any stroke	151 (26.2)	148 (25.7)	2	0.5±2.7	0.88	200
Any disabling stroke	43 (8.0)	51 (8.7)	—	-0.7±1.7	0.56	—
Any stroke or death from any cause	209 (37.0)	208 (36.2)	2	0.8±3.0	0.97	125
Any disabling stroke or death from any cause	113 (21.9)	120 (21.7)	1	0.2±2.6	0.70	500

*Events used to calculate the treatment-failure rate include all strokes (at any site) and all deaths from any cause between randomization and the 30th day after surgery for surgically treated patients and during the 32-day period beginning with randomization for medically treated patients.

†Plus-minus values are percent reductions ±SE. The negative number indicates an increase in risk.

‡P values are derived by comparison of the survival curves by the Mantel-Haenszel chi-square test.

§The number needed to treat is the number of patients who would have to be treated with endarterectomy for one outcome event to be prevented at five years. For ipsilateral stroke at two years, the number needed to treat is 20 for patients with stenosis of 50 to 69 percent and 48 for patients with stenosis of <50 percent. For patients with 70 to 99 percent stenosis, the number needed to treat is eight at both two and five years.

¶Failure rates, expressed as percentages, were derived from Kaplan-Meier estimates of survival at five years.

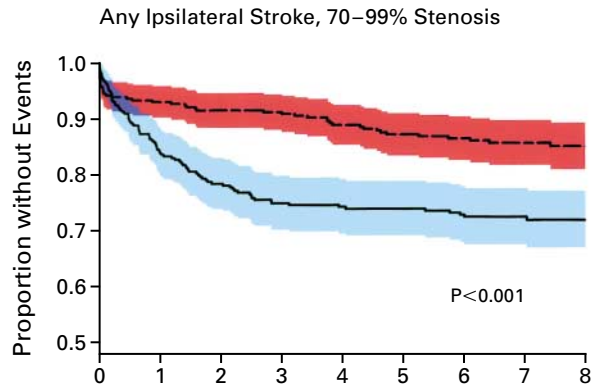
of deaths according to cause (Table 3) did not differ significantly between the two treatment groups. The territory and severity of first strokes are shown in Table 4. The types of first ipsilateral stroke at five years were similar in the two groups (Table 5). Lacunar strokes made up 6.8 percent and 4.1 percent of the events in the medical-therapy and surgical-therapy groups, respectively; strokes of cardioembolic origin accounted for 8.4 percent and 4.8 percent of the events, respectively.

Risk Factors

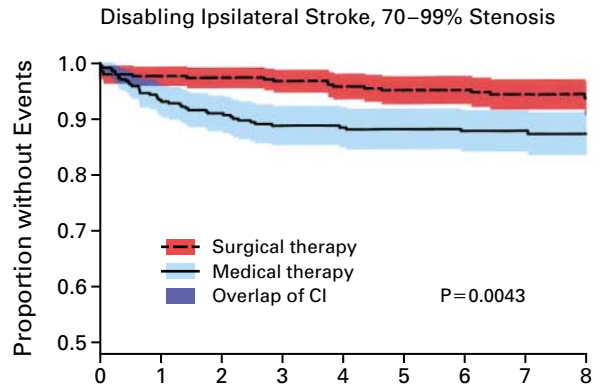
A univariate analysis of all the base-line characteristics listed in Table 1 identified seven characteristics that doubled the perioperative risk of stroke or death (P<0.05). These risk factors and the associated relative risk of any perioperative stroke or death were contralateral carotid occlusion (relative risk, 2.3; 95 percent confidence interval, 1.1 to 5.1), left-sided carotid disease (relative risk, 2.3; 95 percent confidence interval, 1.4 to 3.8), taking less than 650 mg of aspirin per day (relative risk, 2.3; 95 percent

confidence interval, 1.3 to 3.9), the absence of a history of myocardial infarction or angina (relative risk, 2.2; 95 percent confidence interval, 1.3 to 3.8), a lesion present on computed tomography or magnetic resonance imaging ipsilateral to the stenosed artery for which the patient underwent randomization (relative risk, 2.0; 95 percent confidence interval, 1.2 to 3.1), a history of diabetes (relative risk, 2.0; 95 percent confidence interval, 1.2 to 3.1), and diastolic blood pressure above 90 mm Hg (relative risk, 2.0; 95 percent confidence interval, 1.1 to 3.3). Other risk factors, including sex and age, were not statistically significant.

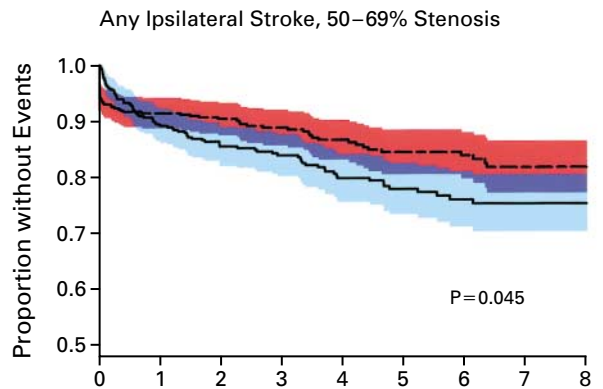
Cox regression analysis identified four characteristics associated with greater long-term benefit of surgery: male sex, a recent stroke, recent hemispheric symptoms, and taking 650 mg or more of aspirin per day. Among patients with stenosis of 50 to 69 percent, the number of patients who needed to be treated with endarterectomy to prevent one ipsilateral stroke of any degree of severity was 12 and the number who needed to be treated to prevent one



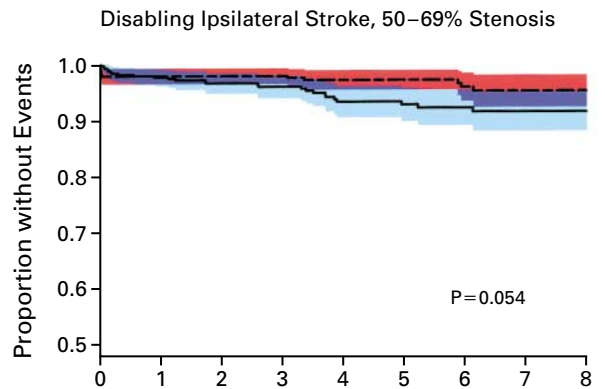
No. AT RISK		0	1	2	3	4	5	6	7	8
Surgical therapy		300	290	281	264	247	224	174	111	
Medical therapy		275	249	230	218	207	192	151	73	



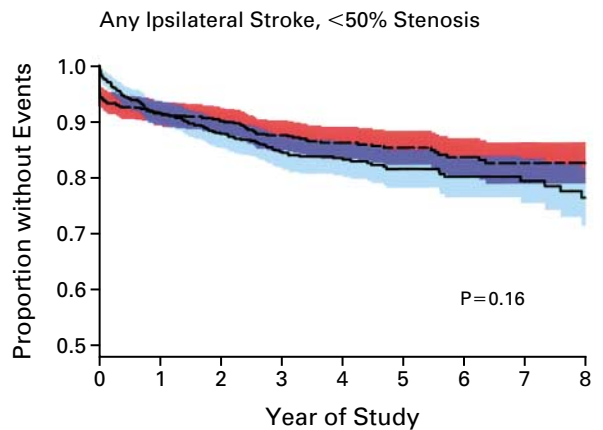
No. AT RISK		0	1	2	3	4	5	6	7	8
Surgical therapy		314	307	297	284	268	247	192	122	
Medical therapy		305	290	272	258	244	229	183	93	



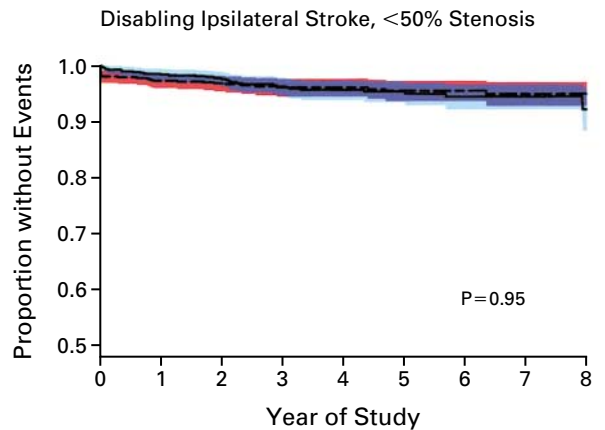
No. AT RISK		0	1	2	3	4	5	6	7	8
Surgical therapy		368	317	261	207	167	134	89	57	
Medical therapy		363	300	248	193	143	110	77	45	



No. AT RISK		0	1	2	3	4	5	6	7	8
Surgical therapy		391	340	284	229	187	145	95	61	
Medical therapy		396	338	280	224	173	133	92	51	



No. AT RISK		0	1	2	3	4	5	6	7	8
Surgical therapy		601	510	407	316	250	168	121	67	
Medical therapy		614	502	406	300	207	142	101	65	



No. AT RISK		0	1	2	3	4	5	6	7	8
Surgical therapy		641	553	443	349	279	190	138	78	
Medical therapy		661	562	465	350	245	167	119	79	

disabling stroke was 16 for men; the corresponding numbers were 67 and 125 for women, 10 and 13 for patients with a recent stroke, 27 and 59 for those with transient ischemic attacks as the qualifying event, 11 and 16 for patients with recent hemispheric symptoms (as compared with negative benefit for patients with retinal symptoms only), 7 and 14 for patients taking 650 mg or more of aspirin per day, and 125 and 44 for those taking less aspirin or none.

The lack of significant benefit among women may be explained by their comparatively low risk of stroke. Among patients with 50 to 69 percent stenosis, the risk of any ipsilateral stroke at five years in the medically treated group was 15 percent for women, as compared with 25 percent for men. Endarterectomy reduced this risk to 14 percent among women and 17 percent among men.

Long-Term Results among Patients with Severe Stenosis

The 326 patients with symptomatic stenosis of 70 percent or more who underwent endarterectomy were followed for an average of eight years. Complete data on outcome events were available for 98.8 percent; four patients were lost to late follow-up. The Kaplan–Meier survival curves (Fig. 3) show the risk of disabling ipsilateral stroke and stroke of any severity in these patients from 30 days to 8 years.

DISCUSSION

Patients with symptomatic carotid stenosis of 70 percent or more (severe stenosis) derive a substantial benefit from endarterectomy that persists for five years or more. The benefit from the procedure is durable. Patients with symptomatic moderate stenosis,

in the range of 50 to 69 percent, benefit less. The overall significance of endarterectomy in preventing ipsilateral stroke was marginal ($P=0.045$). The confidence intervals overlapped in the survival curves at every time point (Fig. 1); the number of such patients who would need to be treated in order to prevent one additional stroke of any degree of severity was double that for patients with stenosis of 70 percent or more. Patients with stenosis of less than 50 percent did not benefit from endarterectomy.

The benefit of endarterectomy was apparent among patients with moderate or severe stenosis within the first two to three years after endarterectomy (Fig. 2). Among medically treated patients, the risk of ipsilateral stroke dropped dramatically to an annual level similar to that among surgically treated patients. If they have no recurring symptoms, patients have little to gain from endarterectomy after two to three years.

The results of recent randomized trials of endarterectomy in patients with symptomatic lesions are in broad agreement. The European Carotid Surgery Trial (ECST),²⁴ which was similar to ours in size, concluded that “carotid endarterectomy is indicated . . . when the symptomatic stenosis is greater than about 80 percent.” A stenosis of 80 percent as measured in ECST is equivalent to 60 percent stenosis determined by the method we used. Our measurements of 30, 40, 50, 60, 70, 80, and 90 percent stenosis correspond to stenoses of 65, 70, 75, 80, 85, 91, and 97 percent, respectively, in ECST.^{25,26} Angiographic conversions are essential for the results of the trials to be compared.²⁷

Caveats apply when our results are extrapolated to the general population of patients with symptoms related to carotid disease. First, the surgeons who participated in our trial were selected for their high level of expertise. If the risk of disabling stroke and death associated with endarterectomy exceeds the levels reported here (2.0 percent), the small benefit of endarterectomy in patients with stenoses of 50 to 69 percent is eliminated, resulting in no benefit. Carotid endarterectomy should be performed only at institutions and by surgeons whose patients have low rates of complications as determined by independent monitoring.

Second, these results do not apply when measurements of stenosis are made with the narrowest portion of the lumen used as the numerator and the carotid bulb or a segment of post-stenotic dilatation as the denominator. Both methods overestimate the severity of stenosis.²¹ It is not clear that measurements obtained by ultrasonography or other noninvasive methods can be substituted for those based on angiography.²⁸ Comparisons of noninvasive studies with angiography must be carried out at individual centers and the use of noninvasive studies validated before angiography is discarded. Nonvalidated ultrasonography frequently overestimates the degree of stenosis,

Figure 1. Kaplan–Meier Curves for Event-free Survival among Patients with Severe and Moderate Stenosis.

The curves show the probability of avoiding an ipsilateral stroke of any degree of severity (left-hand panels) and a disabling ipsilateral stroke (right-hand panels) among patients with carotid stenosis of 70 to 99 percent (top), 50 to 69 percent (center), and less than 50 percent (bottom) who were randomly assigned to undergo carotid endarterectomy (surgical-therapy group) or to receive medical therapy alone (medical-therapy group). Also shown are the P values from the Mantel–Haenszel chi-square test used to compare the survival curves, with the 95 percent confidence interval (CI) for each curve and the overlap between the confidence intervals indicated by bands of color. The numbers below the panels are the numbers of patients in each group who were still at risk during each year of follow-up. These analyses were conducted according to the intention-to-treat principle and include patients who crossed over to the other treatment. The survival curves for medically treated patients differ significantly among the three severity-of-stenosis groups ($P=0.02$ for all ipsilateral strokes and $P<0.001$ for disabling ipsilateral strokes); the curves did not differ significantly for surgically treated patients ($P=0.58$ and $P=0.51$, respectively).

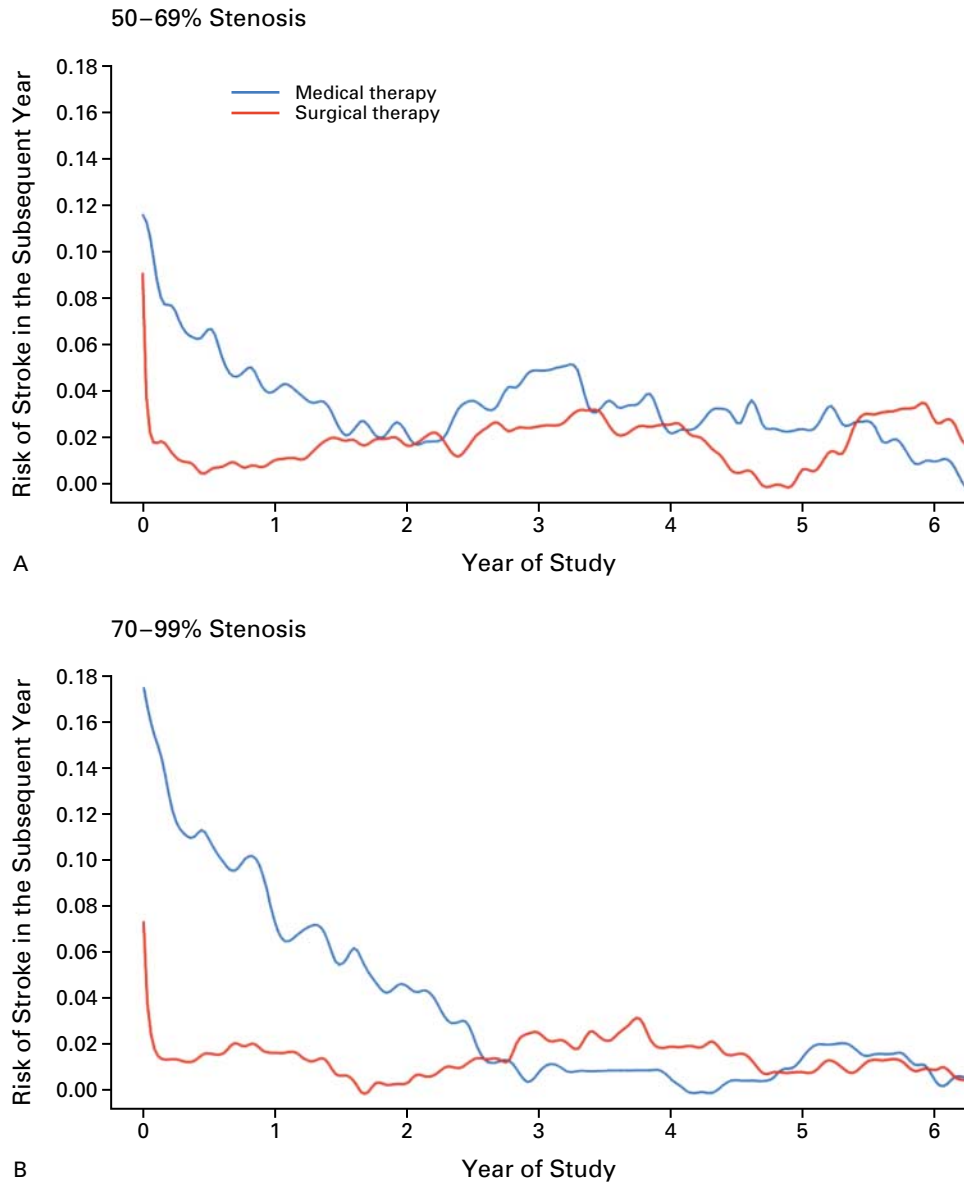


Figure 2. Change in the Risk of Ipsilateral Stroke over Time, According to Severity of Stenosis and Treatment Group. The curves show the risk of an ipsilateral stroke over the next year among patients who had not had an ipsilateral stroke since randomization. Separate calculations were made every 10 days from randomization to the sixth year of follow-up for patients with stenosis of 50 to 69 percent at base line (Panel A) and those with stenosis of 70 to 99 percent at base line (Panel B).

TABLE 3. DEATHS AMONG PATIENTS WITH MODERATE STENOSIS, ACCORDING TO CAUSE AND TREATMENT GROUP.

CAUSE OF DEATH	MEDICAL THERAPY (N=1118)	SURGICAL THERAPY (N=1108)
	no. of patients (%)	
Stroke	24	30
Myocardial infarction	35	32
Other ischemic heart disease	36	34
Sudden death	17	23
Other cardiovascular disease	11	11
Cancer	45	33
Respiratory disease	23	10
Other cause	40	45
Total	231 (20.7)	218 (19.7)

suggesting erroneously that the lesion falls within the range of stenosis known to benefit from endarterectomy. Disabling stroke follows 0.1 percent of angiographic studies; however, inappropriate carotid endarterectomy exposes patients to a 2.0 percent risk of disabling stroke or death.²⁹

Third, although the results of post hoc analyses must be interpreted with caution, base-line risk factors appear to have an important effect on perioperative and long-term outcomes after carotid endarterectomy. Supporting evidence from other large studies of endarterectomy is required, although some confirmatory data are available.³⁰⁻³⁵ Systematic comparisons between the large endarterectomy data bases are now being conducted.

All risk factors must be evaluated when patients with 50 to 69 percent stenosis are being considered for endarterectomy. Patients can be expected to benefit if they have a high risk of stroke over the next two to three years when treated medically and if they are at low risk for stroke after endarterectomy. Observations from both our study and other studies suggest that long-term benefit of surgery is greater and the risk of stroke with medical treatment is higher for men than for women, for patients who have had stroke than for those with transient ischemic attacks, and for patients with hemispheric symptoms than for those with retinal symptoms. These observations also suggest that the risk of perioperative stroke or death is increased in patients with diabetes, elevated blood pressure, contralateral occlusion, left-sided disease, or a lesion that is evident on computed tomography or magnetic resonance imaging.

TABLE 4. TYPE AND SEVERITY OF FIRST STROKES AFTER RANDOMIZATION AMONG PATIENTS WITH MODERATE STENOSIS, ACCORDING TO TREATMENT GROUP.

TYPE OF STROKE	MEDICAL THERAPY (N=1118)			SURGICAL THERAPY (N=1108)		
	NONDIS-ABLING	DIS-ABLING	FATAL	NONDIS-ABLING	DIS-ABLING	FATAL
	no. of patients					
Ipsilateral hemispheric stroke	126	33	6	94	18	7
Ipsilateral retinal stroke	21	0	0	14	0	0
Contralateral hemispheric stroke	39	13	6	48	12	6
Contralateral retinal stroke	7	0	0	5	0	0
Vertebrobasilar stroke	29	6	3	32	10	3
Subarachnoid hemorrhage	0	0	0	0	0	1
Total	222	52	15	193	40	17

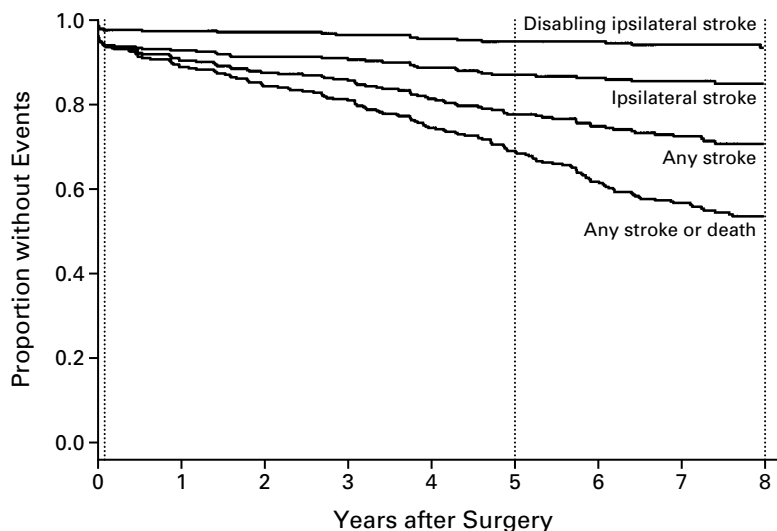
TABLE 5. TYPE OF FIRST IPSILATERAL STROKE OR OTHER EVENT AT FIVE YEARS OF FOLLOW-UP IN PATIENTS WITH MODERATE STENOSIS, ACCORDING TO TREATMENT GROUP.*

EVENT	MEDICAL THERAPY (N=1118)	SURGICAL THERAPY (N=1108)
	no. (%)	
Large-artery hemispheric stroke		
Nonhemorrhagic stroke	121 (63.7)	96 (65.8)
Hemorrhagic infarction	7 (3.7)	6 (4.1)
Large-artery retinal stroke	19 (10.0)	14 (9.6)
Subtotal of events originating in carotid artery	147 (77.4)	116 (79.5)
Lacunar stroke	13 (6.8)	6 (4.1)
Cardioembolic stroke	16 (8.4)	7 (4.8)
Primary intracerebral or subarachnoid hemorrhage	1 (0.5)	4 (2.7)
Death not due to stroke†	1 (0.5)	5 (3.4)
Subtotal of events not originating in the carotid artery	31 (16.3)	22 (15.1)
Uncertain‡	12 (6.3)	8 (5.5)
Total	190 (100.0)	146 (100.0)

*Values for events include all strokes (at any site) and deaths (from any cause) during the 30 days after surgery for surgically treated patients and during the 32 days after randomization for the medically treated patients.

†This category includes only deaths from causes other than stroke in the 30 days after endarterectomy for surgically treated patients and the 32 days after randomization for the medically treated patients.

‡Computed tomography was not performed in these cases.



RISK OF EVENT (%)	30 days	5 years	8 years
Disabling ipsilateral stroke	2.1	5.1	6.7
Ipsilateral stroke	5.8	13.0	15.2
Any stroke	5.8	22.3	29.4
Any stroke or death	5.8	31.0	46.6

Figure 3. Kaplan–Meier Curves for Event-free Survival after Endarterectomy among 326 Patients with Severe Stenosis. The curves show the probability of avoiding an event, according to four different definitions of an outcome event, among patients with 70 to 99 percent stenosis who underwent carotid endarterectomy. Point estimates are shown for the risk of each event at 30 days, 5 years, and 8 years after surgery. The risk of disabling ipsilateral stroke at 30 days includes all perioperative deaths and disabling strokes. The risks of ipsilateral stroke, any stroke, and any stroke or death include all perioperative deaths and all strokes of any type.

Enthusiasm for endarterectomy is increasing.³⁶ In 1996 the operation was performed 130,000 times in the United States, a number double that in 1991 (Pokras RE, National Hospital Discharge Survey: personal communication).³⁷ Many patients with symptomatic stenosis of less than 70 percent will not be considered appropriate candidates for endarterectomy when the risks and benefits are carefully weighed. Our final results do not justify a large increase in the rate of endarterectomy. We recommend restraint.

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APPENDIX

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